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Original Article

Short-Term Insulin Therapy at the Time of Diagnosis of Type 2 Diabetes leads to Better Glycemic Control and Improved Beta Cell Function

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Abstract

Background: Impaired insulin secretion and insulin resistance are the underlying pathophysiological defects in Type 2 diabetes (T2DM) that lead to hyperglycaemia. The β-cell defect in T2DM is usually progressive, leading to eventual β-cell exhaustion and dependence on insulin. It is known that glucotoxicity and lipotoxicity contribute to the initial decreased insulin secretion at the time of diagnosis of T2DM. Therefore, an aggressive approach early in the course of the disease to correct these defects could possibly alter the natural history of T2DM. **Objectives:** Our aim was to study the effect of administration of a short course of insulin therapy at the onset of T2DM on glycaemic parameters and pancreatic β-cell function as assessed by C-peptide estimation. **Materials and Methods:** Treatment-naïve T2DM patients (n = 426) with known duration of diabetes of <3 months were recruited from Dr. Mohan's Diabetes Specialities Centre at Chennai. All patients were treated initially with short-term insulin therapy (4–6 weeks) along with oral hypoglycaemic agents (OHAs), usually metformin alone or sometimes in combination with sulphonylurea. Subsequently, they were continued on diet, exercise and OHA, wherever required. The baseline characteristics, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) and glycated haemoglobin (HbA1c), were compared after (an initial) a mean follow-up period of 2.6 months. Patients were then followed up for another 2 years to evaluate their long-term glycaemic control. Fasting and stimulated C-peptide levels were measured in a subset of patients at baseline and at follow-up at 2–3 months, 1 year and 2 years. **Results:** There was a significant reduction in both FPG and PPG levels. The mean FPG decreased from 214 ± 82 to 111 ± 29 mg/dl ($P < 0.001$), whereas the PPG decreased from 332 ± 120 to 158 ± 54 mg/dl ($P < 0.001$). The HbA1c decreased from 11.8% ± 1.9% to 6.8% ± 1.1% ($P < 0.001$). There was a significant improvement in the serum C-peptide levels, indicating an improvement in β-cell function. The fasting C-peptide levels improved from a mean of 0.85 ± 0.3 to 1.09 ± 0.4 pmol/ml, whereas the stimulated C-peptide value increased from a mean of 1.63 ± 0.8 to 2.09 ± 1.0 pmol/ml even at the end of 2 years after the insulin was discontinued. There was also a favourable change in lipid profile of the patients. Conclusion: Our study demonstrates that, in newly diagnosed T2DM, a short course of insulin therapy given for 4–6 weeks can lead to long-term good glycaemic control and beneficial effects on pancreatic β-cell function, which is sustained up to 2 years.

Keywords: Impaired insulin secretion, insulin resistance, insulin therapy, Type 2 diabetes

Introduction

Impaired insulin secretion and insulin resistance are the underlying pathophysiological defects in Type 2 diabetes (T2DM) that lead to hyperglycaemia. The β-cell defect is usually progressive leading to eventual β-cell exhaustion and dependence on insulin.[1] However, it might be possible to reverse the impaired β-cell function, if intervention is done early in the disease, when the threshold for reversibility has not been passed.[2,3] In recent times, there has been a considerable interest in short-term administration of insulin therapy at the onset of T2DM to counter the underlying β-cell dysfunction.[4] It is known that glucotoxicity and lipotoxicity contribute to the initial decreased insulin secretion at the time of diagnosis

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of T2DM, and it is logical to assume that intensive control of blood glucose early in the natural history of the disorder by intensive insulin therapy can help reverse β-cell dysfunction.[5,6] Current American Diabetes Association guidelines advocate a stepwise approach to diabetes management with the addition of one more antidiabetic agent when the previous one fails and finally adding insulin when all oral hypoglycaemic agents (OHAs) fail! However, this clinical inertia may expose many individuals to prolonged periods of hyperglycaemia and its harmful effects.[7] Several studies[8-11] have shown that a few weeks of aggressive insulin therapy at the onset of T2DM can help attain glycaemic remission for prolonged periods; such an aggressive approach early in the course of the disease could also possibly alter the natural progression, and thus presumably help to prevent complications due to the well-known 'metabolic memory' or 'legacy effect'.[12,13] In this study, we report on the effects of a short course of insulin in Asian Indian patients with newly diagnosed T2DM.

Materials and Methods

A total of 426 treatment-naïve patients T2DM with known duration of diabetes of <3 months were recruited from Dr. Mohan's Diabetes Specialities Centre at Chennai in India. Patients were excluded if they had acute or severe chronic diabetic complications, severe intercurrent illness or tested positive for glutamic acid decarboxylase antibody. All patients meeting the above criteria were enrolled into the study and were given dietary advice which included the caloric intake provided as per the ideal body weight and activity and the need for regular physical activity, i.e., 150 min/week. All the enrolled patients were treated initially with insulin therapy usually at a dose of about 0.2 units/kg/day given once a day along with OHA (usually metformin, plus other oral drugs) if the diabetes was severe, i.e., >9%. The insulin therapy was made more intensive, i.e., twice a day premixed insulin if the glycated haemoglobin (HbA1c) was very high, i.e., >10.5%. Insulin was usually continued for 1–2 months (range 4–6 weeks) until optimal glycaemic control was achieved. Subsequently, they were continued with diet, exercise and OHA, wherever required.

Baseline characteristics included weight, body mass index (BMI), blood pressure, serum creatinine, serum urea, microalbuminuria, fasting lipid profile, fasting and postprandial plasma glucose (PPG), HbA1c and serum C-peptide levels, which were collected at baseline and again after a follow-up of 2–3 months and repeated whenever possible after 1 year and 2 years.

Anthropometric measurements included height and weight measurements, using standardised techniques. BMI was calculated as weight in kilograms divided by height in metre squared. Blood pressure was recorded in the sitting position in the right arm with a mercury sphygmomanometer and rounded off to the nearest 2 mmHg. Two readings were taken 5 min apart, and the mean of the two readings was taken as the blood pressure. Fasting plasma glucose (FPG) (hexokinase method) was measured on Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Serum cholesterol (cholesterol oxidase–peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase–peroxidase-amidopyrine method) and high-density lipoprotein cholesterol (direct method–polyethylene glycol–pretreated enzymes) were measured using Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). Low-density lipoprotein cholesterol was calculated using the Friedewald formula (Friedewald, Levy and Fredrickson, 1972). HbA1C was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA, USA).

Fasting and stimulated (post-breakfast) C-peptide levels were estimated by the electrochemiluminescence method on an Elecsys 2010 machine (Hitachi). To obtain the stimulated C-peptide value, a fasting blood sample was obtained after an overnight fast of at least 8 h and a postprandial sample after 90 min of a standard South Indian breakfast (above 250 cal).[14]

Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all the study participants to use their anonymised medical data.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Estimates were expressed as mean ± standard deviation or proportions. To compare continuous variables, Student's *t*-tests were used, whereas Chi-square tests were used to test differences in proportions. Paired *t*-test was used to compare continuous variables at baseline and follow-up. $P < 0.05$ was considered statistically significant.

Results

A total of 426 patients (male: 243 and female: 183) with new-onset T2DM were included in the study. The characteristics of the study population at baseline and first follow-up, after a mean period of 2.6 months, are tabulated in Table 1. The mean age of the population was 51.7 ± 12.8 years.

There was a significant reduction in both FPG and PPG levels at a mean follow-up period of 2.6 months. The mean FPG came down from 214 ± 82 to 111 ± 29 mg/dl ($P < 0.001$), whereas the PPG decreased from a baseline value of 332 ± 120 to 158 ± 54 mg/dl ($P < 0.001$). The HbA1c decreased from a mean of 11.8% ± 1.9% to 6.8% ± 1.1% ($P < 0.001$).

Overall, by the end of 2.6 months, 58% of individuals achieved good glycaemic control with HbA1c levels <7.0%. It is of interest that 12.7% of individuals achieved HbA1c <5.6%, which is considered as the 'normal' HbA1c level in our population [Figure 1]. Furthermore, 40.9% achieved HbA1c <6.5% on further follow-up and half of those with HbA1c >7.0% at 2.6-month follow-up, achieved HbA1c <7.0%.

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A dramatic reduction in drug dosages was seen. Only one individual of the 426 (0.23%) patients had to be continued on insulin. 13 (3.0%) individuals were managed only on diet alone for the next 1 year, 101 individuals (23.7%) were put on an oral single-drug therapy (usually metformin), 212 (49.7%) individuals required dual-drug therapy (metformin + sulphonylurea or DPP-4 inhibitor) and 99 (23.2%) required triple-drug therapy (metformin + sulphonylurea and DPP-4 inhibitor) in order to maintain HbA1c <7.0%.

We estimated the C-peptide levels at the baseline, i.e., the presentation before they were started on insulin therapy, at the end of 2 months, i.e., after the insulin course was completed and again at the end of 1 year and 2 years.

We had follow-up C-peptide results in all patients at the baseline (n = 426) and in 238 individuals at 2–3 months after stopping the insulin therapy, 186 individuals at 1 year after stopping the insulin therapy and in 96 at 2 years after the insulin therapy. It was heartening to note as shown in Figure 2 that both the fasting and stimulated C-peptide levels dramatically increased immediately after the insulin therapy, and this increase was maintained for up to 2 years after the insulin injections were stopped. In about 20% of the patients, the stimulated C-peptide levels reached values of ≥4.0 pmol/ml, which is in the normal range of individuals without diabetes.

Among the 96 patients followed for up to 2 years after the initial treatment, the mean HbA1c, FPG and PPG were 6.7%, 131 mg/dl and 190 mg/dl, respectively. At the end of 1 year, 4 (4.6%) patients had to be reinitiated on insulin therapy, 40 (41.6%) were continued on single-drug therapy, 38 (39.5%) on dual-drug therapy and 14 (14.5%) were on triple-drug therapy.

Table 1: Characteristics of diabetic patients on intensive insulin therapy at baseline and follow-up after 2.6 months (n=426)

Variables	Baseline	Follow-up	*P*
Age (years)	51.7±12.8	-	-
Gender (n), male:female	243:183	-	-
Weight (kg)	71.0±14.3	71.8±13.8	<0.001
BMI (kg/m^2)	26.8±4.9	27.1±4.7	<0.001
FPG (mg/dl)	214±82	111±29	<0.001
PPG (mg/dl)	332±120	158±54	<0.001
HbA1c (%)	11.8±1.9	6.8±1.1	<0.001
Serum cholesterol (mg/dl)	211±48	148±39	<0.001
Serum triglycerides (mg/dl)	241±210	130±60	<0.001
HDL cholesterol (mg/dl)	39±9	40±9	0.327
LDL cholesterol (mg/dl)	127±35	84±35	<0.001

FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, LDL: Low-density lipoprotein, BMI: Body mass index, HDL: High-density lipoprotein, HbA1c: Glycated haemoglobin

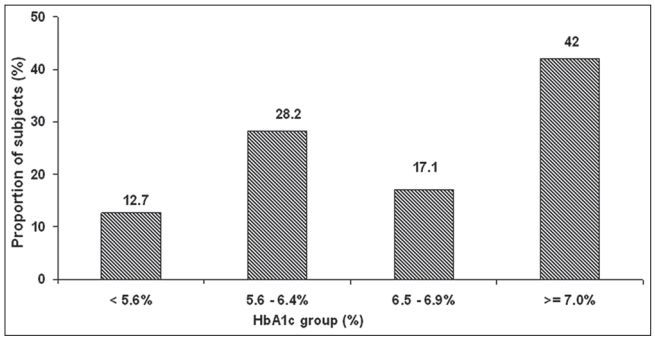

Figure 1: Categorisation of diabetic patients based on glycated haemoglobin at the first follow-up period (after 2.6 months of follow-up)

Discussion

Our results show that excellent glycaemic control could be achieved with short-term insulin therapy given up to 4 weeks in newly diagnosed T2DM. The FPG, PPG and HbA1c values were rapidly corrected to the target range. As many as 12.7% achieved an HbA1c of <5.6%, which is in the non-diabetic range, and 58% of the study population achieved a target HbA1c of <7 at the first follow-up itself. By the end of 6 months, 80% had achieved HbA1c levels <7.0%. Although there was a slight increase in weight (about 1–2 kg on an average), this could be indicative of good glycaemic control due to correction of the mild dehydration and glucolipotoxicity.[15] There was also a favourable response in other parameters such as lipid profile.

The glucotoxicity generated by hyperglycaemia is commonly thought to be the fundamental acquired factor causing continuous decline of β-cell function in T2DM.[3,4] Thus, optimum metabolic control, especially early intensive glycaemic control, can eliminate the deleterious effects of hyperglycaemia and rescue the stunned β-cells,[16] avoiding irreversible loss of β-cell secretory function and β-cell mass. Notably, insulin replacement could provide 'β-cell rest' and reduce excessive secretory demand on the damaged β-cells.[3,17] Weng *et al*.[4] studied the effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed T2DM. In their study, 382 patients were randomised to continuous subcutaneous insulin infusion, multiple daily injection or OHA alone. More patients in the insulin groups achieved target glycaemic control in a shorter time. The remission rates were also higher in the two insulin-treated groups (37.1% and 44.9% vs. 26.7% in the OHA arm). Their study suggested that early, rigorous, glycaemic control by intensive insulin intervention could have more persistent beneficial effects on β-cell function and better long-term glycaemic control than treatment with OHA alone.

Our study showed both short-term and long-term improvement in C-peptide levels, indicating improved β-cell function. Animal studies have demonstrated specific gene alterations in the β-cell after exposure to hyperglycaemia.[18] Our results are also indicative of improved insulin secretion on rapid correction of hyperglycaemia. Insulin action becomes defective after exposure to high blood sugar levels and is correctable on achieving euglycaemia.[19,20] Recent studies show the role of FOX01 in maintaining β-cell function. When there is metabolic

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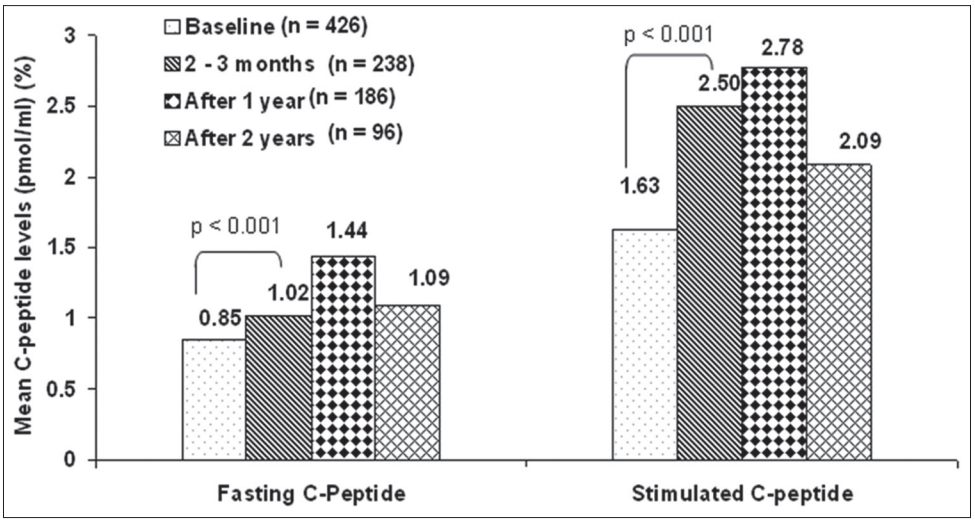

Figure 2: Long-term changes in C-peptide levels after a short course of insulin

stress, β-cells get into a stage of dedifferentiation and get converted to pancreatic α-cells or δ-cells.[21] If the metabolic stress is relieved by instituting early insulin therapy, they again get converted back to β-cells.[22] A study by Kramer *et al*.[23] in patients with newly diagnosed T2DM showed that a short course of intensive insulin therapy is associated with improvement in β-cell function and insulin resistance (assessed by Homeostasis Model Assessment [HOMA]-β and HOMA-Insulin Resistance, respectively). The proportion of participants in drug-free remission 12 months after intensive insulin therapy was about 46%. Ilkova *et al*.[8] also showed that short-term insulin therapy has a good long-term response on β-cell function.

Our results show that the improvement in the β-cell function was maintained even for 2 years after the insulin injections were stopped. Given the natural history of diabetes whereby the insulin secretion continues to decline over time, it is heartening to note that the β-cell function could be maintained up to 2 years after the early and aggressive insulin therapy, showing that it is not only a short-term effect, but also the effect lasts for longer periods of time. Harrison *et al*.[10] also showed that, after a course of insulin injections is given for 3 months, sustained improvement in β-cell function as measured by C-peptide was maintained for 3.5 years. Our study supports these findings.

Assuming that the good metabolic memory or legacy effect may persist for few more years, one can safely assume that a short course of insulin therapy might help in improving the natural history of diabetes with respect to improving β-cell function for several years, thereby preventing the long-term complications of diabetes. However, this is purely speculative at present and more long-term studies have to be done, to prove this.

The ADOPT trial randomly assigned recently diagnosed (<3 years) treatment-naïve patients with diabetes (baseline HbA1c 7.36% ± 0.93%) to monotherapy with metformin, glyburide or rosiglitazone for a median of 4 years.[24] Although glycaemic control improved within the first 6 months, HbA1c increased over the next 3.5 years. This correlated with β-cell function (assessed by HOMA), which also increased in all the groups at 6 months but then declined steadily over the remainder of the study. These results indicate the lack of durability of single-oral drug therapy, even when initial glycaemic control is good. This further supports the case for giving a short-term insulin therapy at the onset of T2DM, especially in those who present with glucotoxicity and lipotoxicity.

Our study has several limitations. All the patients included in our study were treatment naïve, but this does not necessarily mean new-onset T2DM, as many of them could have different durations of undiagnosed diabetes since T2DM has an insidious onset. It is thus possible that the patients who achieved euglycaemia might possibly have had a shorter duration of diabetes, or a lesser severity of the disease. It also explains why all patients did not respond dramatically. The latter could be those with longer duration of undiagnosed diabetes who might have permanently lost β-cell function due to apoptosis of β-cells.

Our study group was heterogeneous in terms of range of FPG and PPG, age (16–81 years) and BMI (16.3–51.3 kg/m^2). Thus, the extent to which the results can be generalised to all patients with T2DM is difficult to predict from the study.

Conclusion

Our study demonstrates that, in newly diagnosed T2DM especially those who present with gluco/lipotoxicity, a short course of insulin therapy can lead to long-term good glycaemic control and possibly beneficial effects on pancreatic β-cell function. Further studies are needed to see the cut points of HbA1c at which early and aggressive insulin therapy would be most beneficial. Furthermore, the long-term durability of β-cell function merits further studies. A large randomised clinical trial comparing early insulin therapy versus multiple oral agents

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used in combination at the time of diagnosis of T2DM would help to throw more light on this.

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Conflicts of interest

There are no conflicts of interest.

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